Amendments to the Claims

Please amend Claims 51 and 52. The Claim Listing below will replace all prior versions of the claims in the application:

Claim Listing

1. (original) A method of treating a patient suffering from a condition mediated by release of a proinflammatory cytokine comprising

treating said patient with a cholinergic agonist selective for an α7 nicotinic receptor in an amount sufficient to decrease the amount of the proinflammatory cytokine that is released from a macrophage

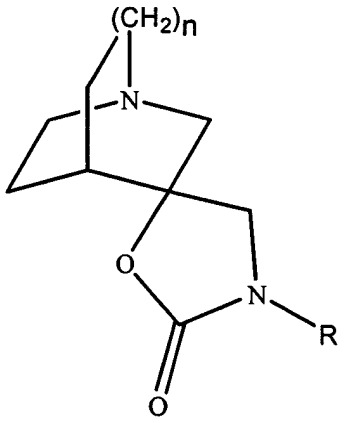
wherein said condition is selected from the group consisting of appendicitis, peptic, gastric and duodenal ulcers, peritonitis, pancreatitis, epiglottitis, achalasia, cholangitis, cholecystitis, hepatitis, Whipple's disease, asthma, allergy, anaphylactic shock, immune complex disease, organ ischemia, reperfusion injury, organ necrosis, hay fever, sepsis, septicemia, endotoxic shock, cachexia, hyperpyrexia, eosinophilic granuloma, granulomatosis, sarcoidosis, septic abortion, epididymitis, vaginitis, prostatitis, urethritis, bronchitis, emphysema, rhinitis, cystic fibrosis, pneumonitis, pneumoultramicroscopic silicovolcanoconiosis, alvealitis, bronchiolitis, pharyngitis, pleurisy, sinusitis, influenza, respiratory syncytial virus infection, herpes infection, HIV infection, hepatitis B virus infection, hepatitis C virus infection, disseminated bacteremia, Dengue fever, candidiasis, malaria, filariasis, amebiasis, hydatid cysts, burns, vasulitis, angiitis, endocarditis, arteritis, atherosclerosis, thrombophlebitis, pericarditis, myocarditis, myocardial ischemia, periarteritis nodosa, rheumatic fever, coeliac disease, congestive heart failure, adult respiratory distress syndrome, chronic obstructive pulmonary disease, meningitis, encephalitis, neuritis, neuralgia, spinal cord injury, paralysis, uveitis, arthritides, arthralgias, osteomyelitis, fasciitis, Paget's disease, gout, periodontal disease, rheumatoid arthritis, synovitis, myasthenia gravis, thryoiditis, systemic lupus erythematosus, Goodpasture's syndrome, Behcets's syndrome, allograft

rejection, graft-versus-host disease, ankylosing spondylitis, Berger's disease, ankylosing spondylitis, Berger's disease, Retier's syndrome, and Hodgkins disease.

2. (original) The method of claim 1, wherein the proinflammatory cytokine is selected from the group consisting of tumor necrosis factor (TNF), interleukin (IL)-1β, IL-6, IL-18 and HMG-1.

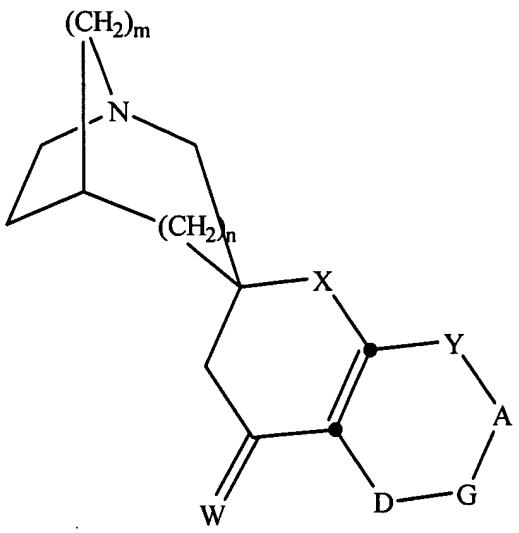
3. (original) The method of claim 1, wherein the proinflammatory cytokine is TNF.

4. (original) The method of claim 1, wherein the cholinergic agonist is selected from the group consisting of a quaternary analog of cocaine; (1-aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid 1-(2-fluorophenyl)-ethyl ester; a compound of formula I:



I

wherein, R represents hydrogen or methyl, and
n represents 0 or 1; a pharmaceutically acceptable salt of a compound of formula I; a compound of formula II:



II

wherein:

m is 1 or 2,

n is 0 or 1,

Y is CH, N or NO,

X is oxygen or sulfur,

W is oxygen, H_2 or F_2,

A is N or $C(R^2)$,

G is N or $C(R^3)$,

D is N or $C(R^4)$,

with the proviso that no more than one of A, G and D is nitrogen but at least one of Y, A, G and D is nitrogen or NO,

R^1 is hydrogen or C_1-C_4 alkyl,

R^2, R^3 and R^4 are independently hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, aryl, heteroaryl, OH, OC_1-C_4 alkyl, CO_2R_1, -CN, $-NO_2$, $-NR_5R_6$, $-CF_3$ or $-OSO_2CF_3$, or R^2 and R^3, R^3 and R^4, respectively, may together form another six membered aromatic or heteroaromatic ring sharing A and G, or G and D, respectively, containing between zero and two nitrogen atoms, and substituted with one to two of the following substitutents: independently hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-

C_4 alkynyl, aryl, heteroaryl, OH, OC_1-C_4 alkyl, CO_2R^1, -CN, $-NO_2$, $-NR^5R^6$, $-CF_3$ or $-OSO_2CF_3$,

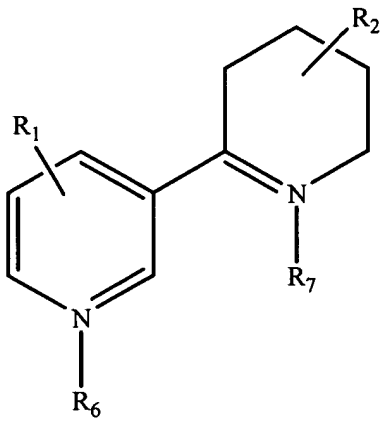
R^5 and R^6 are independently hydrogen, C_1-C_4 alkyl, $C(O)R^7$, $C(O)NHR^8$, $C(O)OR^9$, SO_2R^{10} or may together be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{11},

or a bond,

j is 2 to 7,

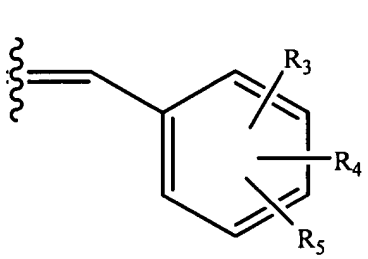
k is 0 to 2,

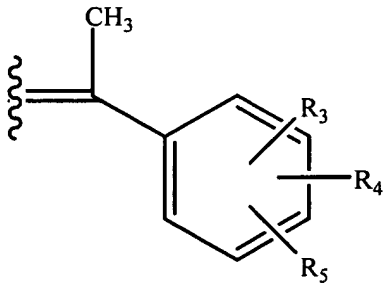
R^7, R^8, R^9, R^{10} and R^{11} are independently C_1-C_4 alkyl, aryl, or heteroaryl, or an enantiomer thereof; a pharmaceutically acceptable salt of a compound of formula II; a compound of formula III:

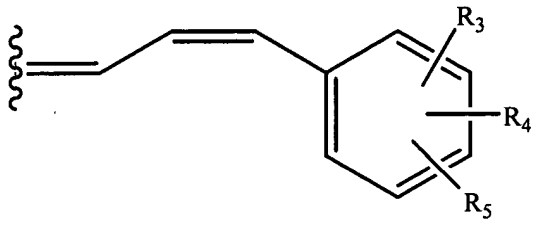


III

wherein R_1, R_6 and R_7 are hydrogen or C_1-C_4 alkyl, and R_2 is selected from a group of

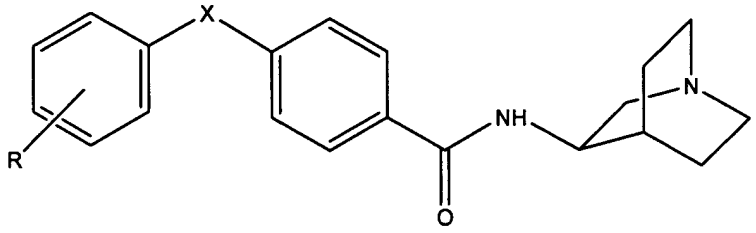






and

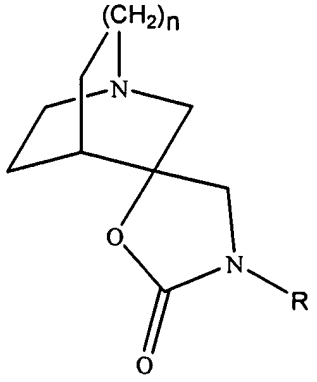
wherein, R_3, R_4 and R_5 are selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, C_1-C_6 alkoxy optionally substituted with N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, carboalkoxy having 1 to 4 carbons in the alkoxy, amino, amido having 1 to 4 carbons in the acyl, cyano, and N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, halo, hydroxyl or nitro; and a compound of formula IV:



IV

wherein X is O or S, and R is selected from the group consisting of H, OR_1, $NHC(O)R_1$, and a halogen, wherein R_1 is a C_1-C_4 alkyl.

5. (original) The method of claim 1, wherein the cholinergic agonist is a compound of formula I:



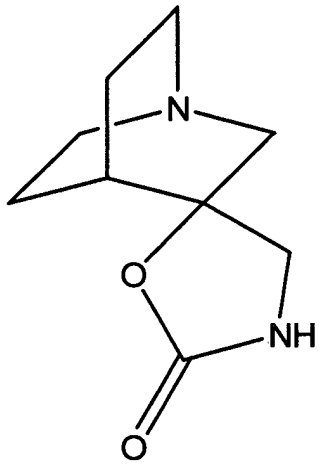
I

wherein, R represents hydrogen or methyl, and

n represents 0 or 1;

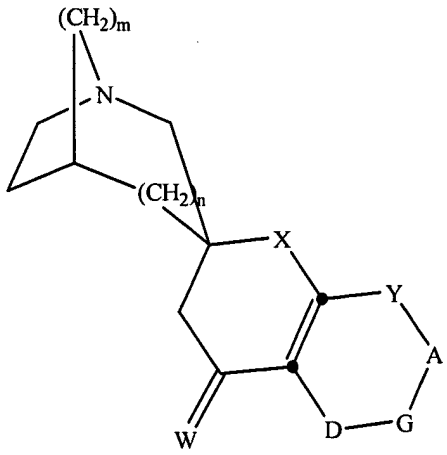
or a pharmaceutically acceptable salt thereof.

6. (original) The method of claim 5, wherein the cholinergic agonist is (-)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one]



(VII).

7. (original) The method of claim 1, wherein the cholinergic agonist is a compound of formula II:



II

wherein:

m is 1 or 2;

n is 0 or 1;

Y is CH, N or NO;

X is oxygen or sulfur;

W is oxygen, H_2 or F_2;

A is N or $C(R^2)$;

G is N or $C(R^3)$;

D is N or $C(R^4)$;

with the proviso that no more than one of A, G and D is nitrogen but at least one of Y, A, G and D is nitrogen or NO;

R^1 is hydrogen or C_1-C_4 alkyl;

R^2, R^3 and R^4 are independently hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, aryl, heteroaryl, OH, OC_1-C_4 alkyl, CO_2R_1, -CN, $-NO_2$, $-NR_5R_6$, $-CF_3$ or $-OSO_2CF_3$, or R^2 and R^3, R^3 and R^4, respectively, may together form another six membered aromatic or heteroaromatic ring sharing A and G, or G and D, respectively, containing between zero and two nitrogen atoms, and substituted with one to two of the following substitutents: independently hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, aryl, heteroaryl, OH, OC_1-C_4 alkyl, CO_2R^1, -CN, $-NO_2$, $-NR^5R^6$, $-CF_3$ or $-OSO_2CF_3$;

R^5 and R^6 are independently hydrogen, C_1-C_4 alkyl, $C(O)R^7$, $C(O)NHR^8$, $C(O)OR^9$, SO_2R^{10} or may together be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{11}, or a bond;

j is 2 to 7;

k is 0 to 2;

R^7, R^8, R^9, R^{10} and R^{11} are independently C_1-C_4 alkyl, aryl, or heteroaryl,

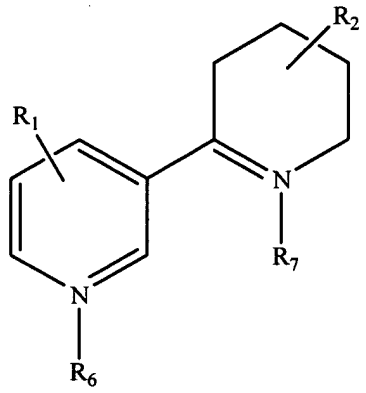
or an enantiomer thereof,

or a pharmaceutically acceptable salts thereof.

8. (original) The method of claim 7, wherein the cholinergic agonist is a compound of formula II wherein m is 1; n is 0; p is 0; x is oxygen; A is $C(R^2)$; G is $C(R^3)$; and D is $C(R^4)$.

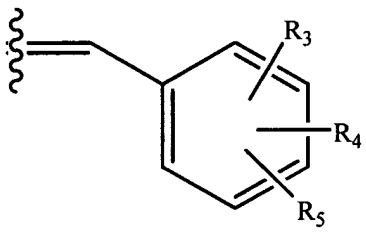
9. (original) The method of claim 7, wherein the cholinergic agonist is 5'-phenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridin].

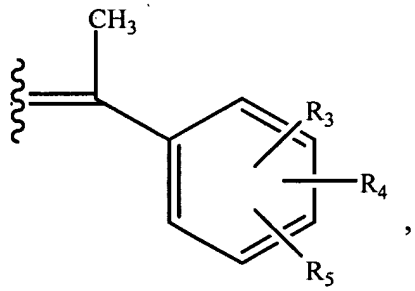
10. (original) The method of claim 1, wherein the cholinergic agonist is a compound of formula III:



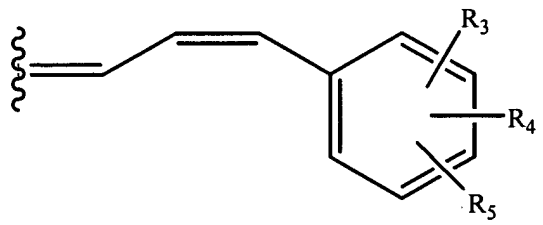
(III)

wherein R_1, R_6 and R_7 are hydrogen or C_1-C_4 alkyl; and R_2 is selected from a group of





,



and

wheren, R_3, R_4 and R_5 are selected from the group consisting of hydrogen, C_1-C_4 alkyl optionally substituted with N,N-dialkylamino having 1 to 4 carbons in each of the alkyls,

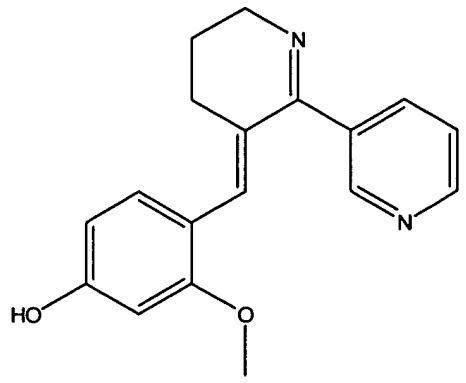
C_1-C_6 alkoxy optionally substituted with N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, carboalkoxy having 1 to 4 carbons in the alkoxy, amino, amido having 1 to 4 carbons in the acyl, cyano, and N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, halo, hydroxyl or nitro.

11. (original) The method of claim 10, wherein the cholinergic agonist is a compound of formula III, wherein R_2 is attached to the 3-position of the tetrahydropyridine ring, and further wherein R_3, which is attached to the 4- or the 2- position of the phenyl ring, is selected from the group consisting of amino, hydroxyl, chloro, cyano, dimethylamino, methyl, methoxy, acetylamino, acetoxy, and nitro.

12. (original) The method of claim 10, wherein the cholinergic agonist is a compound selected from the group consisting of formula III, wherein R_3 is hydroxyl, and wherein R_1, R_4, and R_5 are hydrogen; formula III, wherein R_3 is acetylamino and wherein R_1, R_4, and R_5 are hydrogen; formula III, wherein R_3 is acetoxy and wherein R_1, R_4, and R_5 are hydrogen; formula III, wherein R_3 is methoxy, and wherein R_1, R_4, and R_5 are hydrogen; formula III, wherein R_3 is methoxy and wherein R_1 and R_4 are hydrogen, and further wherein R_3 is attached to the 2-position of the phenyl ring, and R_5, which is attached to the 4-position of the phenyl ring, is methoxy or hydroxy.

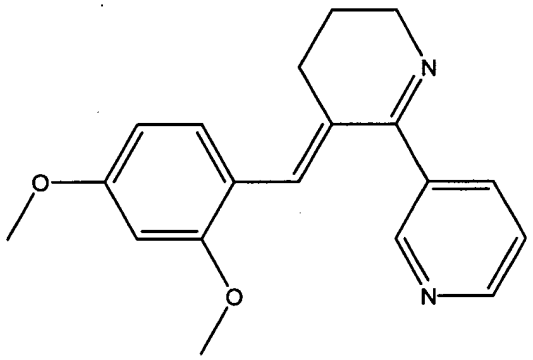
13. (original) The method of claim 10, wherein the cholinergic agonist is is selected from the group consisting of 3-2,4-dimethoxybenzylidine anabaseine (DMXB-A), 3-(4-hydroxybenzylidene)anabaseine, 3-(4-methoxybenzylidene)anabaseine, 3-(4-aminobenzylidene)anabaseine, 3-(4-hyrdoxy-2-methoxybenzylidene)anabaseine, 3-(4-methoxy-2-hydroxybenzylidene)anabaseine, trans-3-cinnamylidene anabaseine, trans-3-(2-methoxy-cinnamylidene)anabaseine and trans-3-(4-methoxycinnamylidene)anabaseine.

14. (original) The method of claim 10, wherein the cholinergic agonist is 3-(4-hydroxy-2-methoxybenzylidene)anabasine



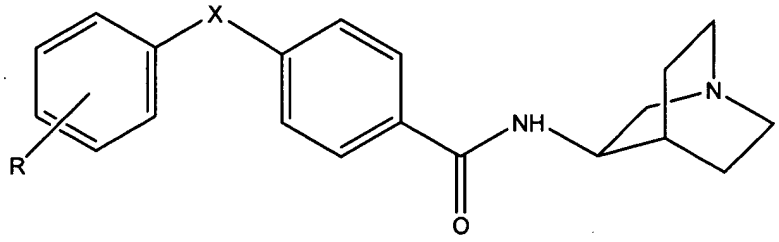
(VI).

15. (original) The method of claim 10, wherein the cholinergic agonist is 3-(2,4-dimethoxybenzylidene)anabaseine.



(V).

16. (original) The method of claim 1, wherein the cholinergic agonist is a compound of formula IV:



IV

wherein X is O or S; and

R is selected from the group consisting of H, OR_1, $NHC(O)R_1$, and a halogen, wherein R_1 is a C_1-C_4 alkyl.

17. (original) The method of claim 15, wherein the cholinergic agonist is selected from a group consisting of N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(4-hydroxyphenoxy)benzamide, N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(4-acetamidophenoxy)benzamide, N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(phenylsulfanyl)benzamide, and N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(3-chlorophenylsulphonyl)benzamide.

18. (original) The method of claim 15, wherein the cholinergic agonist is N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(phenylsulfanyl)benzamide.

19. (original) The method of claim 1, wherein the cholinergic agonist is cocaine methiodide.

20. (original) The method of claim 1 wherein the condition is selected from the group consisting of appendicitis, peptic, gastric and duodenal ulcers, peritonitis, pancreatitis, hepatitis, asthma, allergy, anaphylactic shock, organ necrosis, hay fever, sepsis, septicemia, endotoxic shock, cachexia, septic abortion, disseminated bacteremia, burns, coeliac disease, congestive heart failure, adult respiratory distress syndrome, chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosis, myocardial ischemia, spinal cord injury, paralysis, allograft rejection and graft-versus-host disease.

21. (original) The method of claim 1 wherein the condition selected from the group consisting of appendicitis, peptic, gastric or duodenal ulcers, peritonitis, pancreatitis, hepatitis, asthma, allergy, anaphylactic shock, organ necrosis, hay fever, sepsis, septicemia, endotoxic shock, cachexia, septic abortion, disseminated bacteremia, burns, congestive heart failure, adult respiratory distress syndrome, chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosis, myocardial ischemia, cerebral infarction, cerebral embolism, spinal cord injury, paralysis, allograft rejection or graft-versus-host disease.

22. (original) The method of Claim 1 wherein the condition is selected from the group consisting of peritonitis, pancreatitis, sepsis, endotoxic shock, adult respiratory distress syndrome, chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus

erythematosis, myocardial ischemia, allograft rejection, asthma, graft-versus-host-disease, congestive heart failure and cystic fibrosis.

23. (original) The method of claim 1, wherein the condition selected from the group consisting of peritonitis, pancreatitis, sepsis, endotoxic shock, cachexia, adult respiratory distress syndrome, chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosis, myocardial ischemia, and allograft rejection.

24. (original) The method of claim 1, wherein the condition is sepsis.

25. (original) A method for determining whether a compound is a cholinergic agonist selective for an α7 nicotinic receptor, the method comprising

determining whether the compound inhibits release of a proinflammatory cytokine from a mammalian cell, and

determining whether the compound is a cholinergic agonist reactive with at least one nicotinic receptor that is not α7,

wherein a compound that inhibits the release of the proinflammatory cytokine from the mammalian cell, but is not a cholinergic agonist reactive with at least one nicotinic receptor that is not α7, is a cholinergic agonist selective for an α7 nicotinic receptor.

26. (original) The method of claim 25, wherein the proinflammatory cytokine is selected from the group consisting of tumor necrosis factor (TNF), interleukin (IL)-1β, IL-6, IL-18 and HMG-1.

27. (original) The method of claim 25 wherein the proinflammatory cytokine is TNF.

28. (original) The method of claim 25 wherein the mammalian cell is an immune cell.

29. (original) The method of claim 25 wherein the mammalian cell is a macrophage.

30. (original) The method of claim 25 further comprising treating the mammalian cell with an agent that stimulates a proinflammatory cytokine cascade.

31. (original) The method of claim 30, wherein the agent is LPS.

32. (original) The method of claim 25 wherein the determination of inhibition of proinflammatory cytokine release comprises measurement of mRNA of the proinflammatory cytokine.

33. (original) The method of claim 25 wherein the determination of inhibition of proinflammatory cytokine release comprises measurement of the proinflammatory cytokine protein.

34. (original) The method of claim 25 wherein the determination of inhibition of proinflammatory cytokine release comprises measurement of proinflammatory cytokine activity.

35. (original) A method for determining whether a compound is a cholinergic antagonist reactive with an α7 nicotinic receptor, the method comprising determining whether the compound reduces the ability of a cholinergic agonist to inhibit the release of a proinflammatory cytokine from a mammalian cell,

wherein a compound that reduces the ability of a cholinergic agonist to inhibit the release of a proinflammatory cytokine from a mammalian cell is a cholinergic antagonist reactive with an α7 receptor.

36. (original) The method of claim 35, wherein the proinflammatory cytokine is selected from the group consisting of tumor necrosis factor (TNF), interleukin (IL)-1β, IL-6, IL-18 and HMG-1.

37. (original) The method of claim 35, wherein the proinflammatory cytokine is TNF.

38. (original) The method of claim 35, wherein the mammalian cell is an immune cell.

39. (original) The method of claim 35, wherein the mammalian cell is a macrophage.

40. (original) The method of claim 35, further comprising treating the mammalian cell with an agent that stimulates a proinflammatory cytokine cascade.

41. (original) The method of claim 40, wherein the agent is LPS.

42. (original) The method of claim 35, wherein the determination of whether the compound reduces the ability of the cholinergic agonist to inhibit the release of a proinflammatory cytokine from a mammalian cell comprises measurement of mRNA of the proinflammatory cytokine.

43. (original) The method of claim 35, wherein the determination of whether the compound restrains the ability of the cholinergic agonist to inhibit the release of a proinflammatory cytokine from a mammalian cell comprises measurement of the proinflammatory cytokine protein.

44. (original) The method of claim 35, wherein the determination of whether the compound restrains the ability of the cholinergic agonist to inhibit the release of a proinflammatory cytokine from a mammalian cell comprises measurement of proinflammatory cytokine activity.

45. (original) A method for determining whether a test compound has the ability to inhibit inflammation, the method comprising determining whether the test compound is a cholinergic agonist reactive with an α7 nicotinic receptor.

46. (original) The method of claim 45, wherein the receptor is on a macrophage.

47. (original) A method for determining whether a test compound has the ability to inhibit inflammation, the method comprising determining whether the test compound inhibits binding of an antagonist to an α7 nicotinic receptor.

48. (original) The method of claim 47, wherein the antagonist to an α7 receptor is bungarotoxin.

49. (original) An oligonucleotide or mimetic capable of inhibiting attenuation of lipopolysaccharide-induced TNF release from a mammalian macrophage upon exposure of the macrophage to a cholinergic agonist, wherein the oligonucleotide or mimetic consists essentially of a sequence greater than 5 nucleotides long that is complementary to an mRNA of an α7 receptor.

50. (original) The oligonucleotide or mimetic of claim 49, wherein the sequence is complementary to a transcription initiation region of the mRNA.

51. (currently amended) The oligonucleotide of claim 49, wherein the sequence comprises 5'-gcagcgcatgttgagtcccg-3' (SEQ ID NO: 19).

52. (currently amended) The oligonucleotide or mimetic of claim 49, wherein the sequence consists essentially of 5'-gcagcgcatgttgagtcccg-3' (SEQ ID NO: 19).

53. (original) A method of inhibiting attenuation of TNF release from a mammalian macrophage upon exposure of the macrophage to a cholinergic agonist, the method comprising treating the macrophage with the oligonucleotide or mimetic of claim 49.

54. (original) The method of claim 53, wherein the macrophage is in a mammal.

55. (original) The method of claim 54, wherein the mammal is a human.